AMENDMENT TO THE CLAIMS

The present amendment amends claims 1, 3, 6, 8, 10, 11, 14, 26, 27, 28 and 29; cancels claims 2 and 32; and adds claim 38. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the following claims are in the case:

1. (Currently Amended) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising:

(a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided dry powder form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and comprising a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and cholesteryl palmitate, and

(b) an antiasthma drug,

wherein ingredients (a) and (b) are provided in a form for administration together or separately and ~~the product~~ at least ingredient (a) is arranged for delivery of at least one individual inhalable dose, the individual dose or each individual dose comprising said ingredient (a) in an inhalable amount of at least 25mg, for forming an adsorbed layer of phospholipid extending over the surfaces of the lungs and air passages.

Claim 2 presently canceled

3. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which medicament (a) comprises said first component and said second component in a weight ratio of from 1:9 to 9:1.

4. (Original) A combination product as claimed in claim 3, in which the proportion by weight of said first component exceeds that of said second component.

5. (Original) A combination product as claimed in claim 4, in which said first component and said second component are present in a weight ratio of from 6:4 to 8:2.

6. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which the medicament (a) comprises a phosphatidyl glycerol.

7. (Original) A combination product as claimed in claim 6, in which the phosphatidyl glycerol comprises one or more diacyl phosphatidyl glycerols, of which at least a proportion of the acyl groups are unsaturated.

8. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines.

9. (Original) A combination product as claimed in claim 8, in which the medicament (a) comprises dipalmitoyl phosphatidyl choline.

10. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which the medicament (a) is in micronised form.

11. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which said medicament (a) has a median particle size not exceeding 10μm.

12. (Original) A combination product as claimed in claim 11, in which said medicament (a) has a median particle size not exceeding 5μm.

13. (Original) A combination product as claimed in claim 12, in which said medicament (a) has a median particle size of less than 3 μm.

14. (Currently Amended) A combination product as claimed in claim ~~2~~ 1, in which the antiasthma drug comprises one or more respiratory drugs selected from the group consisting of β_2-agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists.

15. (Previously Presented) A combination product as claimed in claim 14, which comprises one or more of said antiasthma drugs in an amount of up to 10 parts by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

16. (Previously Presented) A combination product as claimed in claim 15, which comprises one or more of said respiratory drugs in an amount of up to one part by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

17. (Previously Presented) A combination product as claimed in claim 14, in which ingredient (b) comprises a β_2-agonist.

18. (Previously Presented) A combination product as claimed in claim 14, in which ingredient (b) comprises a steroid.

19. (Previously Presented) A combination product as claimed in claim 14, in which ingredient (b) comprises a cromone.

20. (Previously Presented) A combination product as claimed in claim 14, in which ingredient (b) comprises a leukotriene receptor antagonist.

21. (Previously Presented) A combination product as claimed in claim 14, in which ingredient (b) comprises an antimuscarinic drug.

22. (Previously Presented) A combination product as claimed in claim 1, wherein the individual dose or each individual dose comprises said ingredient (a) in an inhalable amount of at least 40mg.

23. (Previously Presented) A combination product as claimed in claim 36, wherein the product is arranged for delivery of ingredient (a) in an inhalable amount of at least 25mg.

24. (Previously Presented) A combination product as claimed in claim 37, wherein the product is arranged for delivery of ingredient (a) in an inhalable amount of at least 25mg.

25. (Previously Presented) A combination product as claimed in claim 1, in which at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

26. (Currently Amended) A combination product as claimed in claim 1 ~~or claim 2~~, in which the antiasthma drug is arranged for delivery in admixture with ingredient (a).

27. (Currently Amended) A combination product as claimed in claim 1 ~~or claim 2~~, in which the antiasthma drug is arranged for delivery separately from, and simultaneously or sequentially with, ingredient (a).

28. (Currently Amended) A pack for use as part of a combination product according to claim 1 ~~or claim 2~~, said pack including a delivery device for delivery of ingredient (a) to a patient and further comprising instructions to use said delivery device in a method of treatment including the separate simultaneous or sequential administration of an antiasthma drug.

29. (Currently Amended) A method of prevention and/or treatment of asthma, comprising administering to a patient at least one dose of a combination product as defined in claim 1 ~~or claim 2~~.

30. (Previously Presented) A delivery device for administering to a patient by inhalation a medicament for the prevention and/or treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances the spreading of the

medicament, the delivery device being arranged for delivery of at least one individual dose of the SAPL composition in an inhalable amount of at least 25mg.

31. (Previously Presented) A delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament comprising a first component consisting of one or more phosphatidyl cholines and a second component consisting of one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate, the delivery device being arranged for delivery of at least one individual inhalable dose, the or each individual dose comprising said first component and said second component in a combined inhalable amount of at least 25mg.

Claim 32 presently canceled

33. (Previously Presented) A delivery device as claimed in claim 30 or 31, which further includes means for dispensing an inhalable dose of an antiasthma drug.

34. (Previously Presented) A medicament for use in the control of asthma, comprising (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug, wherein the medicament is arranged for delivery of said SAPL composition in an individual inhalable dosage amount of at least 25mg.

35. (Previously Presented) A combination product for use in the prevention or treatment of asthma comprising

(a) a medicament comprising a first phospholipid component which is capable of binding to lung tissue and a second component which is capable of enhancing the spreading of said first component over an aqueous medium at 37°C, said medicament being in the form of a finely divided powder; and

(b) an antiasthma drug;

the ingredients (a) and (b) being arranged for administration in combination or separately, simultaneously or sequentially, to deliver ingredient (a) in an individual inhalable dosage amount of at least 25mg.

36. (Previously Presented) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and (b) an antiasthma drug, wherein ingredients (a) and (b) are provided in a form for separate, simultaneous or sequential, administration and wherein ingredient (a) consists of a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate.

37. (Previously Presented) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal

mammalian body temperature and (b) an antiasthma drug selected from the group consisting of β_2-agonists, cromones, antimuscarinic drugs and leukotriene receptor antagonists, wherein ingredients (a) and (b) are provided in a form for administration together or in a form for administration separately and wherein ingredient (a) consists of a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate, said first component and said second component being present in a weight ratio of from 6:4 to 8:2.

38. (New) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising:

(a) a medicament comprising a phospholipid composition in finely divided dry powder form having surfactant properties which enable it to spread rapidly over the surfaces of the lungs and air passages, the phospholipid composition including a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and cholesteryl palmitate; and

(b) an antiasthma drug;

wherein ingredients (a) and (b) are provided for administration together or separately and at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the individual dose or each individual dose comprising said ingredient (a) in an inhalable amount of at least 25mg.

RESPONSE

I. Status of the Claims

Prior to the second Action, claims 1-37 were pending and have been examined. The second Action withdraws each previous rejection and enters a single new rejection. Finality was likely improper in light of the new rejection, but is not contested (**Section VII**).

Presently, claims 1, 3, 6, 8, 10, 11, 14, 26, 27, 28 and 29 have been amended without prejudice, to reflect certain preferred embodiments of the invention. Claims 2 and 32 have been canceled without prejudice. Claim 38 has been added, which is unified with the examined claims and fully supported by the present and parent applications.

Claims 1, 3-31 and 33-38 are therefore in the case. According to the revisions to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Applicants' Telephone Interview Summary

After considering the second Action, a number of telephone interviews were held between the Applicants and Examiner Haghighatian. The main interview was held on December 02, 2003 between Examiner Haghighatian, Applicants' undersigned representative, Shelley Fussey, Derek Woodcock (inventor) and Applicants' European patent representative, Ceris Humphreys. Applicants appreciate the examiner's time and the guidance provided.

During the interview, Dr. Woodcock explained certain important features of the invention and highlighted some of the key differences over the cited art. Examiner Haghighatian helpfully suggested that strengthening the functional features in the claims would assist in overcoming the remaining rejection. Although agreement was not reached regarding possible claim language, Applicants have acted upon the examiner's suggestion and currently amended the claims to include functional features, as discussed during the interview. Applicants also submit the

declaration of Dr. Robert Price, which attests to the surprising differences and advantages of the presently claimed invention over the cited art.

As the enclosed declaration addresses matters in considerable detail, Applicants presently submit a succinct response. The remarks in Applicants' earlier response are also specifically incorporated herein by reference. The present actions are being taken without acquiescing with the outstanding rejection and simply in order to progress the application to allowance as timely as possible, particularly in light of patent term issues.

As agreed during the interview, should Examiner Haghighatian have any remaining concerns after consideration of the present amendment, response and declaration, Applicants respectfully request that the examiner telephone Applicants' undersigned representative to discuss any further steps believed to be necessary to secure allowance.

III. Entry of Amendments

The present amendments are entitled to entry as a matter of right in light of the concurrent Request for Continued Examination (RCE).

IV. Support for the Claims

Support for the revised claims and the new claim exists throughout the specification and claims of the original and parent applications. In light of the canceled claims, no fees should be due for entry of the new claim. However, any fees deemed necessary for the new claim should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/ 4040.000300.

In claim 1, the "wherein" clause has been revised to recite the function of the SAPL composition in forming an adsorbed layer of phospholipid extending over the surfaces of the

lungs and air passages[1]. Support for this language exists throughout the specification, such as at page 3, with particular support at page 3, lines 20-30.

Part (a) of claim 1 has been revised to further define the SAPL composition as being in finely divided "dry powder" form, as supported throughout the specification, such as at page 3, particularly at page 3, lines 3-6. Also in claim 1, part (a), the SAPL composition is now defined as in previous claim 2, *i.e.*, as including a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and cholesteryl palmitate.

Part (b) of claim 1 has been revised to specify that "at least ingredient (a)" is arranged for delivery of at least one individual inhalable dose, which is supported throughout the specification, such as in claims 22 and 23 from the PCT phase.

Claim 2 has been canceled without prejudice, as this language is now included in claim 1.

Each of claims 3, 6, 8, 10, 11, 14, 26, 27, 28 and 29 have been amended to remove the reference to claim 2, presently canceled.

Claim 32 has also been canceled, as referring only to claim 2.

New claim 38 is based upon claim 1, but includes alternative functional language in the form of "having surfactant properties which enable it to spread rapidly over the surfaces of the lungs and air passages". Support for claim 38 also exists throughout the original and parent applications, such as in the present specification at page 3, particularly at page 3, lines 1-3.

It will therefore be understood that no new matter is included within any of the revised claims or the new claim.

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[1]For ease of review, part (a), part (b) and the wherein clause of claim 1 have been presented as separate paragraphs, although these changes are not "amendments".

V. Rejections Overcome

The former rejection of claims 1-35 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,895,719 to Radhakrishnan *et al.* ("Radhakrishnan") in view of U.S. Patent No. 5,306,483 to Mautone ("Mautone") has been overcome and withdrawn.

The former rejection of claims 1, 2 and 6-35 under 35 U.S.C. § 103(a) as allegedly being obvious over PCT publication WO 96/19199 to Byström & Nilsson has also been overcome and withdrawn. Applicants appreciate these developments.

VI. Rejection of Claims 1-37 Under 35 U.S.C. § 103(a)

Claims 1-37 are newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Radhakrishnan and Mautone documents in further view of U.S. Patent No. 5,925,334 to Rubin & Newhouse ("Rubin"). Finality is believed to be improper, but is not contested (**Section VII**). Although Applicants respectfully traverse, the rejection is overcome.

As Rubin issued after the present priority date (November 26, 1998), it is only potentially available as prior art under 35 U.S.C. § 102(e) as of its own filing date. Therefore, the following response should not be interpreted as an acquiescence that the § 102(e) date of Rubin is earlier than Applicants' date of invention.

The present invention concerns therapeutic combination products, medicaments, packs, delivery devices and associated methods for use in the prevention and/or treatment of asthma. As discussed in the telephone interview, an important feature of the present invention is that relatively *large* doses of an SAPL composition (as defined in the claims) in *finely divided dry powder* form can be generated and administered to patients. The relatively large amounts of SAPL composition form an adsorbed layer of phospholipid extending over the surfaces of the lungs and air passages (*e.g.*, see specification at pages 3-4, 20-25 and Example). The use of

relatively high doses of the SAPL composition means that, for a given surface area available, the mean depth or thickness of the resultant adsorbed layer will be greater than in the case of relatively small administered doses of SAPL composition. As detailed herein, these and other aspects of the presently claimed invention would not have been obvious to one of ordinary skill in the art in light of Radhakrishnan, Mautone and Rubin, even if properly combined.

In addition, Applicants provide the declaration of Dr. Robert Price, who has particular expertise in the area of pharmaceutical surface science and particle engineering in pulmonary drug delivery. The Price declaration clearly sets out why the ordinary skilled artisan would not have been led by Radhakrishnan to use dosages of SAPL composition of 25mg or more, and why the ordinary skilled artisan would not, even after reference to Mautone and/or Rubin, reasonably have modified the teaching of Radhakrishnan to arrive at the dry powder, high SAPL dosage products of the claimed invention.

A. The References have been Improperly Combined

It is noted that the earlier § 103(a) rejection over Radhakrishnan and Mautone has been withdrawn. The Office has thus indicated that claims 1-37 are patentable over Radhakrishnan and Mautone in combination. Important questions to answer, therefore, are (1) whether the combination of Radhakrishnan, Mautone and Rubin is proper; and (2) whether the addition of Rubin cures the lack of teaching or suggestion in Radhakrishnan and Mautone. Applicants address these issues in turn, in addition to rebutting the rejection as a whole.

Before the P.T.O. may combine the disclosure of two or more prior art references in order to establish a *prima facie* case of obviousness, there must be some teaching, suggestion or motivation to combine the references. *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). Here, the references have been improperly combined, including the improper combination of

Radhakrishnan and Mautone, and the new addition of Rubin. As the Office has not set forth sufficient evidence to support the proposed combination, the rejection is *prima facie* improper.

Applicants earlier pointed out why Radhakrishnan and Mautone would not be viewed together by one of ordinary skill in the art. For example, Radhakrishnan concerns slow drug release, whereas Mautone is concerned with achieving rapid spreading over a surface. Radhakrishnan is also seeking to improve liposome behavior, whilst Mautone is concerned with non liposomal forms of behavior. The Price declaration also discusses these issues in explaining that it would not have been obvious for one of ordinary skill in the art to combine Radhakrishnan and Mautone (Price declaration at paragraph 9).

Applicants also traversed the rejection over Radhakrishnan and Mautone on the basis that, even if combined, the proposed combination did not teach or suggest the claimed invention and did not provide the required reasonable expectation of success, and that the invention had surprising and unexpected features. The rejection was withdrawn.

The Action now adds Rubin in an attempt to cure the deficiencies of Radhakrishnan and Mautone. However, the combination of Radhakrishnan, Mautone and Rubin has not been supported and is, in fact, improper. The Price declaration at paragraph 10 explains why the combination of Radhakrishnan and Rubin would not have been reasonably considered by one skilled in the art. Starting from Radhakrishnan, significantly increasing the amount of lipid material would significantly lower the amount of encapsulated drug, leading to poor dose reproducibility. Thus, the combination of Radhakrishnan with Rubin would not have been contemplated by one of ordinary skill in the art prior to the present invention.

The three cited references, which have significantly different content and purposes, have thus been improperly combined and the rejection is *prima facie* improper and should be withdrawn.

B. The References in Combination do not Teach or Suggest the Invention

The proposed combination is improper (see above). Even if combined, Radhakrishnan, Mautone and Rubin do not teach or suggest the presently claimed invention and do not provide the reasonable expectation of success required under § 103(a). *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988).

Applicants respectfully refer to the Price declaration, which explains, based upon scientific evidence, why Radhakrishnan, Mautone and Rubin, even in combination, would not have taught or suggested the presently claimed invention to one of ordinary skill in the art at the time the invention was made (summarized in Price declaration at paragraphs 11, 12, 13 and 31). In particular, Dr. Price explains that Radhakrishnan, Mautone and Rubin, even in combination, do not teach or suggest the high phospholipid dosages of the claimed invention or the formation of a relatively thick barrier coating. He also explains that, based on the prior use of phospholipids as mere delivery vehicles or surfactants (Price declaration at paragraphs 14-16), the present inventors' use of high dose phospholipids as active ingredients in antiasthma medications was a surprising advance in this field (see, *e.g.*, Price declaration at paragraph 5 and paragraph 13).

As described in the specification and in Applicants' first response, the finely divided SAPL formulations of the present invention give rise to a protective effect, which enhances the therapeutic effect of an antiasthma drug. For optimum results, a relatively high dose of the SAPL composition is required, as recited in the pending claims. The second Action agrees that "Radhakrishnan lacks disclosure on high doses of phospholipids and on the weight ratios for the components" (second Action at page 4)[2]. The Action contends, however, that Mautone and

[2]Contrast this clear acknowledgement that Radhakrishnan lacks an important element of the claimed invention with the later allegation that Radhakrishnan "teaches the exact same product" [as the claimed invention] (second Action at page 8).

Rubin cure these deficiencies in Radhakrishnan. In contrast, and as explained by Dr. Price, it would not have been obvious for one of ordinary skill in the art to have modified Radhakrishnan by adding the component ratios as taught by Mautone (see, *e.g.*, Price declaration at paragraphs 26 and 27) or doses taken from Rubin (see, *e.g.*, Price declaration at paragraphs 29 and 30).

It is agreed that Radhakrishnan aims to modulate the rate of drug release (second Action at page 7), whereas Mautone concerns spreading agents (second Action at page 8). Rather than supporting the rejection, Mautone provides no motivation to change the Radhakrishnan compositions. As stated in the Price declaration at paragraph 26, why would the skilled artisan seeking improved control of drug release according to Radhakrishnan, that is by means of controlling release of the drug from liposomes, seek to modify the disclosure in view of Mautone, which would apparently result in a product in which that control was lost? Thus, rather than following the conventional wisdom, the present inventors have proceeded *contrary* to the accepted wisdom, which is further evidence of non-obviousness. *In re Hedges*, 228, USPQ 685, 687 (Fed. Cir. 1986).

Turning to Rubin, the Action contends that it would have been obvious for one of ordinary skill in the art, given the alleged teachings of Radhakrishnan and Mautone on lower dosages of phospholipids, "to have looked in the art for higher doses, as taught by Rubin, in order to obtain more effective results, especially since Radhakrishnan teaches that effects of liposomes are dose-related" (second Action at page 6). This proposal is also based on flawed reasoning.

As described in the Price declaration at paragraphs 29 and 30, modifying the liposomes of Radhakrishnan to have a lipid component according to Rubin would be contra-indicated, in part due to problems with dose reproducibility in relation to the drug. Indeed, by attempting to apply the lipid composition of Rubin to Radhakrishnan, it is by no means clear that liposomes

would even be formed, which would further deter the reader of Radhakrishnan from proceeding with modification according to Rubin (Price declaration at paragraph 30). The prior art thus teaches away from the invention, which is clear evidence of patentability.

In common with Mautone, Rubin also fails to teach or suggest a medicament comprising an SAPL composition in finely divided dry powder form, as required by the claimed invention. The present specification teaches the importance of finely divided dry powders (see, *e.g.*, specification at pages 2 and 3), which overcomes difficulties in prior art documents such as Mautone and Rubin (also discussed in the Price declaration at paragraph 30).

As summarized by Dr. Price, Radhakrishnan, Mautone and Rubin, even in combination, would thus not teach or suggest the claimed invention to one of ordinary skill in the art at the time the invention was made, and would not provide a reasonable expectation of success.

It is well established under the law that the examiner, the Board or a court should not substitute their own speculations for factual knowledge of those skilled in the art, as set forth in an affidavit. *In re Katzschmann*, 146 USPQ 66, 68 (C.C.P.A. 1965). Therefore, even if the Office was held to have established a proper *prima facie* case, the present response and the declaration of Dr. Price are more than sufficient to rebut the rejection. *In re Katzschmann, supra*; *In re Soni*, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995); *Schendel v. Curtis*, 38 USPQ2d 1743.

The rejection of all claims under § 103(a) is therefore overcome on various grounds and should be withdrawn.

VII. New Ground of Rejection Rendered Finality Improper

The second Action included a new ground of rejection under 35 U.S.C. § 103(a), citing a combination of documents including the Rubin patent, new to the record. The reliance on a newly-cited document as part of a new combination renders the second Action prematurely final under MPEP 706.07(a).